Hypersensitivity Reactions

Introduction

The concept of "hypersensitivity type" confuses most people. If you FIRST learn the mechanisms, the causal agents, and the cells involved . . . then memorize the "type" label, you'll be much better off when it comes to interpreting what type of sensitivity reaction is in front of you. In this lesson we describe only how to identify the different types of hypersensitivity reactions, and name them by their cell type and mechanism. At the very end, after you've learned the types without associating a number to them, THEN you learn the "type number." In subsequent lessons we use this information and refer back to it in order to discuss transplant biology and autoimmune disease, and their corresponding pharmacology.

Mast Cells: IgE-Mast Cell Mediated Hypersensitivity

First of all, a little bit of vocabulary. Allergen is simply an antigen that leads to an IgE-mediated reaction. You will see allergen and antigen mentioned interchangeably in this section. When we are talking about an IgE antibody, the thing IgE's Fab portion binds to can be called **an antigen or an allergen**.

The first time the body comes into contact with an allergen, nothing much happens. The APCs present an antigen to the T_H0 cells, inducing them to go down either the T_H1 or the T_H2 path. In the case of IgE, the T_H0 cells have taken the T_H2 path, so that is our focus in this section. T_H2 cells secrete cytokines (IL-4) that tell B cells to make **IgE**. This means there is an isotype-switch, affinity maturation, etc., just like any T-cell-mediated B-cell activation. T_H2 cells also make IL-5, which increases production of mast cells and eosinophils. So, to summarize what we just said, T_H2 cells secrete IL-4 that causes B cells to make IgE, and also secrete IL-5 that causes an increase in mast cells and eosinophils. These two products come together as a team that will allow for hypersensitivity reactions to occur. Note that even though IgE is made by B cells, hypersensitivity is not caused by B cells. It is caused by the IgE the B cells produce, and that IgE sits on a mast cell, waiting for an antigen to bind to it and trigger a reaction. We will go over this in more detail below, but that's the big picture to get first. If you have the big picture, then you can fine tune it with details.

The one T_H2 response produces IgE and mast cells. IgE and mast cells together cause allergen-mediated hypersensitivity.

After the body has encountered an antigen for the first time, the body has been **sensitized**. The initial response to an allergen may be mild or undetectable. All that has happened is that an APC has presented to a T cell and that T cell has told a B cell to isotype-switch and produce IgE. Now that the body has been sensitized, it is ready to recognize and react to the allergen. The allergen is the enemy. Once the immune system recognizes it, there is a rapid and potentially systemic reaction. Therefore, the second and subsequent exposures can be severe and catastrophic. This is why "mild" reactions to antibiotics or to vaccinations are taken so seriously. It is impossible to predict whether a subsequent exposure to something one is allergic to will result in a more severe reaction than in the past.

IgE is secreted from plasma cells. That IgE would simply disappear quickly and be eliminated from the body were it not for stabilization on a mast cell. IgE circulates, looking for a mast cell to pair up with. Once it finds a mast cell, it attaches its **Fc portions to the mast cell** membrane (and by the way, it also binds to basophil membranes in a similar way). The circulating immunoglobulins, secreted by plasma cells, become membrane-bound surface proteins attached to mast cells. When a mast cell has IgE on its surface, it is considered **primed**. The Fc portion of IgE sticks into the cytoplasm of the mast cell and the Fab portion sticks out from the surface of the mast cell, available for allergen to bind to it. When that allergen "returns" because of re-exposure of the body to that allergen, the IgE Fab is ready for it. The allergen binds to two IgE molecules on the surface, called **cross-linking of IgE**. The cross-linking of

IgE molecules on the mast cell sends a signal into the cytoplasm that leads to **mast-cell degranulation**. More simply put, it is a chain of events: antigen stimulates the Fab portion of two IgE molecules, the Fc portion does something to the mast cell, and there go the granules.

Degranulation releases potent and **immediately active** vasoactive compounds (**histamine** is the most important) that lead to **vasodilation**, increased vascular permeability, and **bronchoconstriction**. When the degranulation remains local, the vasoactive compounds give rise to the symptoms of common allergic diseases such as "nasal allergies": runny nose, watery eyes, itching, sneezing; and of asthma: coughing, wheezing, shortness of breath.

If this degranulation is widespread, **anaphylaxis** results. Anaphylaxis is a systemic allergic reaction. Massive vasodilation throughout the body all at once causes **hypotension**. Histamine released everywhere causes **an itchy rash** (this rash is called urticaria, or hives). In the lungs, the response to release of mast cell contents is bronchoconstriction, which can lead to cough, wheezing, and shortness of breath. Patients may also experience angioedema, which is a rapid swelling of the tissues in certain parts of the body. Most commonly this will be seen in the head and neck, and when it affects the laryngeal airway it can be life-threatening. While someone experiencing anaphylaxis is unlikely to die due to bronchoconstriction (such as in asthma) or due to urticaria, they may die from laryngeal edema or hypotension if treatment is not provided. In addition, urticaria and symptoms of bronchoconstriction are sometimes the early signs of anaphylaxis. If epinephrine is not provided to these patients, they may progress to demonstrating other more life-threatening symptoms. Epinephrine is therefore given to patients with systemic reactions in order to halt the progression of anaphylaxis and restore systemic vascular resistance.

In anaphylaxis, give epinephrine to restore blood pressure. Epinephrine also helps with opening the airways.

Degranulation also releases longer-lasting slower-onset **eosinophilic chemotactic agents**, such that more chronic conditions (where the reaction is constantly occurring or recurring) such as asthma or allergic rhinitis can present with eosinophils and necrosis on tissue biopsy.

Hours later, a **delayed** and substantially **more potent effect** is induced by products from the **arachidonic acid pathway**, such as **leukotrienes** and **prostaglandins**. The stimulus to produce leukotrienes and prostaglandins comes from the same mast-cell signaling that caused degranulation. The effect is the same—increased permeability, bronchoconstriction—but it takes longer (hours) and lasts longer. So histamine and other substances released by the immediate degranulation cause the immediate symptoms of allergy, while the leukotrienes and prostaglandins, produced upon mast-cell signaling, cause a more delayed and longer-lasting reaction.

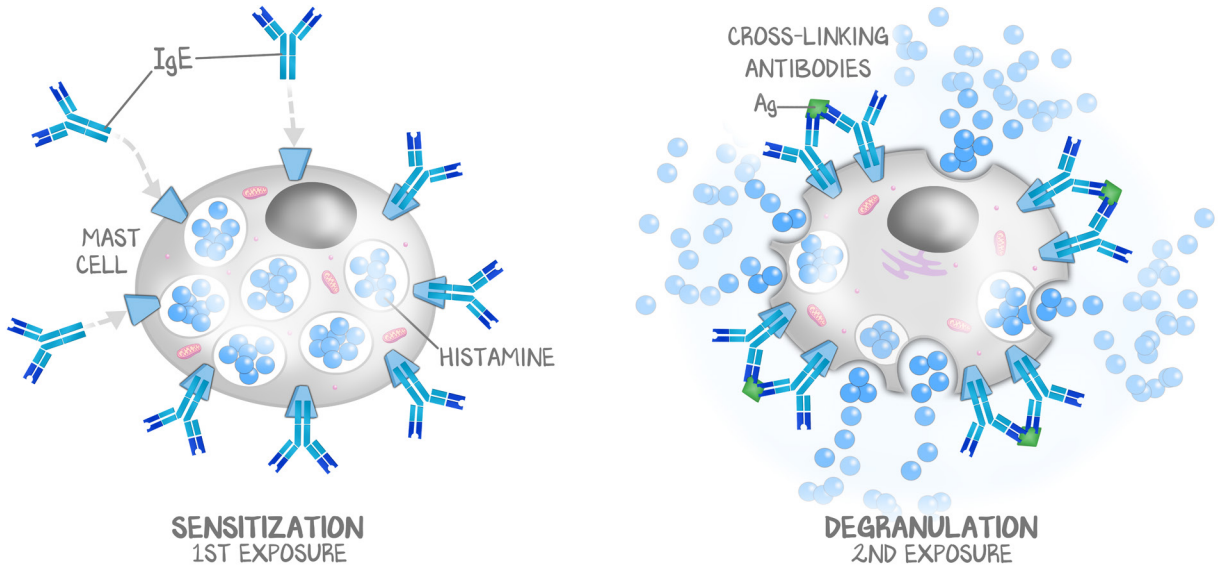

Figure 11.1: Mast-Cell Degranulation
On first exposure, sensitization, plasma cells are formed that create IgE specific to the antigen. There is no reaction at this point, but the antibody and mast cell come together; the Fc portion of IgE is stabilized in the membrane of mast cells. Upon re-exposure, antigen cross-links neighboring IgE antibodies that are on the mast cell surface. These antibodies act like receptors and send a signal to the mast cell cytoplasm, inducing degranulation.

Remember, the function of mast cells and basophils is to expedite the expulsion of organisms too large for phagocytosis. It isn't surprising that when the immune system reacts to a harmless environmental allergen, the patient experiences flushing (vasodilation), runny nose and nasal congestion (vasodilation), or GI hypermotility (diarrhea). Bronchoconstriction, smooth muscle contraction of the small airways of the lung, may result from either a local reaction or as part of a systemic reaction to an allergen.

ALLERGIC DISEASE	ALLERGENS	CLINICAL
Seasonal allergies	Trees, grass, dust, dander	Edema and inflammation of nasal mucosa, rhinorrhea, itchy/watery eyes, pharyngeal cough
Anaphylaxis	Stings, medications, food are common (but any allergen can cause anaphylaxis)	Hypotension, diffuse urticaria and/or angioedema, itching, vomiting, diarrhea, symptoms of bronchoconstriction (cough, wheeze, shortness of breath)
Asthma	Inhaled particles	Wheezing, cough, shortness of breath
Urticaria	Local or systemic exposure to an allergen	Local edema, rash, itching, wheal and flare reaction

Table 11.1: IgE-Mediated Diseases

B Cells: Antibody-Mediated against Host Cells

Antibodies were designed to prevent cellular function by preventing cell contact (neutralization), enhance phagocytosis of the innate immune system (opsonization), and increase the activity of the complement cascade. This was achieved by secreting antibodies that bound to the surface of target pathogens. The Fab portion binds to the antigen, and the Fc region binds to phagocytes or the complement proteins of the complement cascade.

So what happens when an antibody is created that is against a host cell? Yep: neutralization, opsonization, complement activation. Only these malicious antibodies aren't doing what they're supposed to—they're supposed to be antibodies against foreign antigens. Instead, they're antibodies against host tissue. These are called **auto-antibodies**. These are almost always IgG, and IgG can cross the placenta and the blood-brain barrier. This process of antibodies causing cellular destruction like they always do, except this time to self, is called **cytotoxic antibody-mediated** hypersensitivity.

But in addition to the process of neutralization, opsonization, and complement, which involves antibody binding to cell membranes, antibody can also be specific to receptors on cell membranes. This means that if they bind to that receptor, it can cause the *receptor* to be either activated or inhibited. **Anti-receptor antibodies** can have an **agonist effect** (as in Graves' disease, which induces the thyroid to make more T_4), or they can have an **antagonist** effect (as in myasthenia gravis). The point is that in the case of an anti-receptor antibody, no phagocytosis or complement is involved; instead, the antibody disrupts the function of the receptor. This antibodies-causing-no-destruction-but-instead-altering-function is called **noncytotoxic antibody-mediated** hypersensitivity.

Antibodies bind and target dies? Cytotoxic antibody-mediated. Antibodies bind and target lives? Noncytotoxic antibody-mediated.

That sounds suspiciously like two very different mechanisms, both caused by circulating antibodies. Indeed, two very different mechanisms; and yet guess who decided that these two separate mechanisms (cytotoxic antibodies and noncytotoxic antibodies) should be the classified the same? Yep. We did. The medical profession. Either antibodies bind, leading to cell-mediated destruction of the thing the antibody is made against, OR antibodies bind and alter the function of a receptor. Receptors don't die. Cells do.

CYTOTOXIC ANTIBODY DISEASE		
DISEASE	**ANTIBODY**	**SYNDROME**
Autoimmune hemolytic anemia	IgM (cold) against RBC proteins IgG (warm) against RBC proteins	RBCs die = hemolysis ⟶ anemia
Thrombocytopenic thrombotic purpura	IgG against platelets	Thrombocytopenia = bleeding (FAT RN*)
Goodpasture's	IgG against basement membrane of glomerulus and alveoli	Hemoptysis and hematuria
Rheumatic fever (post-strep heart)	IgG against antistreptolysin-O that cross-reacts with heart antigens	Myocarditis, arthritis, valvular stenosis
Hemolytic disease of the newborn	Rh^- Mom and 1st Rh^+ Baby = IgM Rh^- Mom and 2nd Rh^+ Baby = IgG	Sensitization, IgM cannot cross placenta Fetal anemia, IgG can cross placenta Give IVIg on 1st pregnancy
NONCYTOTOXIC ANTIBODY DISEASE		
DISEASE	**ANTIBODY**	**SYNDROME**
Myasthenia gravis	Postsynaptic AChR, competitive inhibition at postsynaptic plate	Small muscle weakness, repeated use *induces* fatigue
Lambert-Eaton	Presynaptic Ca, requires more action potentials to overcome	Large muscle weakness, repeated use *improves* weakness
Graves' disease	TSH-receptor on thyroid, stimulates receptor, ↑ T_4	Hyperthyroidism, goiter, exophthalmos
Pernicious anemia	Antibody against parietal cells of the gut, prevents intrinsic factor, prevents B_{12} absorption	Macrocytic anemia

Table 11.2: Antibody-Mediated Autoimmune Disease
*FAT RN = Fever, Anemia, Thrombocytopenia, Renal, Neuro (TTP pentad mnemonic). See Heme/Onc: Clotting #4: *Platelet Bleeding.*

The third type of hypersensitivity, immune-complex deposition, is also because of antibodies—but is classified differently from cytotoxic and noncytotoxic antibody responses. With cytotoxic and noncytotoxic antibody-mediated responses, the antibodies go to the target tissue and DO SOMETHING to that tissue. But in immune-complex deposition, the antibodies don't act on the target cell or organ, they react to a small piece of circulating antigen and then they get stuck everywhere because the complex (Ab + Ag) is too big to get through places where the individual components might have been able to get through.

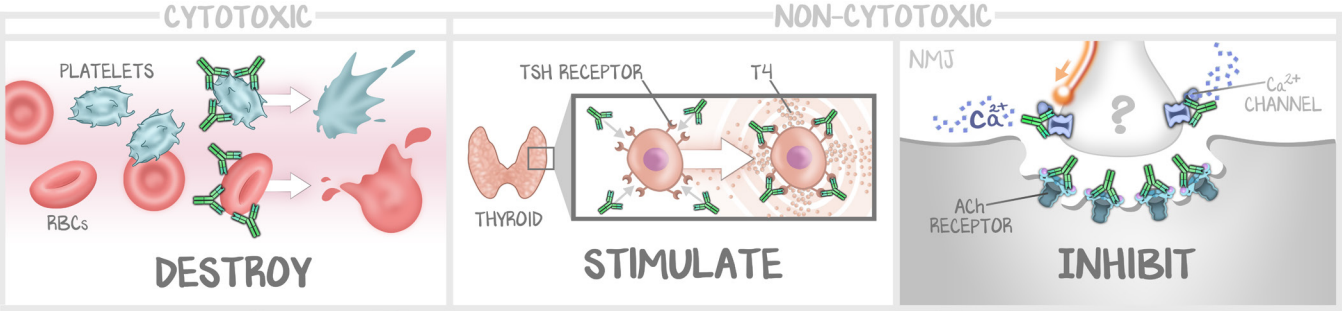

Figure 11.2: Antibody-Mediated Autoimmune Disease
Can either be cytotoxic, where the Fc portion summons the usual immune response, and the antibody has marked good tissue for death; or noncytotoxic, where the Fc portion doesn't matter, and it just happens that the Fab portion binds a receptor to either stimulate it (Graves') or inhibit it (myasthenia gravis, Lambert-Eaton).

B-Cell Immune-Complex Deposition Hypersensitivity

Immune-complex hypersensitivity is also based on **antibody formation**. However, the antigen is not at the organ of origination. That is, the antigen isn't necessarily still attached to the cell from which it came. It means that there's no cell to kill, opsonize, neutralize, summon complement to, etc. However, the antigen-antibody complex is large, so it gets filtered out in the small vasculature, where it gets stuck, or **deposited**.

Wherever these immune complexes get deposited is where inflammation occurs. The innate immune system is drawn to the site of deposition (phagocytes still see Fc portions sticking out at them and want to eat whatever the Fc's are attached to), then attempts to clear the antigen-antibody complexes, often taking with them whatever they got deposited into. Complement activation still happens (Fc presentation); innate immune cells still show up (Fc presentation). Just like in antibody-mediated hypersensitivity, except that in immune-complex hypersensitivity, there's no cell attached to the antigen; instead, it's just some other normal tissue that this antibody-antigen complex happened to get stuck in.

Because these antigen-antibody complexes are soluble and small, they form anywhere, and are carried throughout the bloodstream only to get deposited in whichever organ was unfortunate to have them get stuck there. That means **immune-complex deposition disease** has a **systemic involvement** and often affects the **joints**, **lungs**, and the **kidneys**. However, there's rarely an organ that has the antigen, and almost never is that organ alone attacked (if so, it would be antibody-mediated).

IMMUNE-COMPLEX DEPOSITION		
DISEASE	**ANTIBODIES**	**SYMPTOMS**
Lupus	Antinuclear antibodies, dsDNA antibodies, antihistone antibody	Arthritis, butterfly malar rash, nephritis
Post-strep glomerulonephritis	Antistreptolysin-O (ASO) antibodies deposit	Hematuria, HTN, renal failure
Serum sickness	ABO antibodies	Flu-like reaction, TRALI

Table 11.3: Immune-Complex Deposition
A table of specific disease processes that arise from the formation of an antigen-antibody complex deposition.

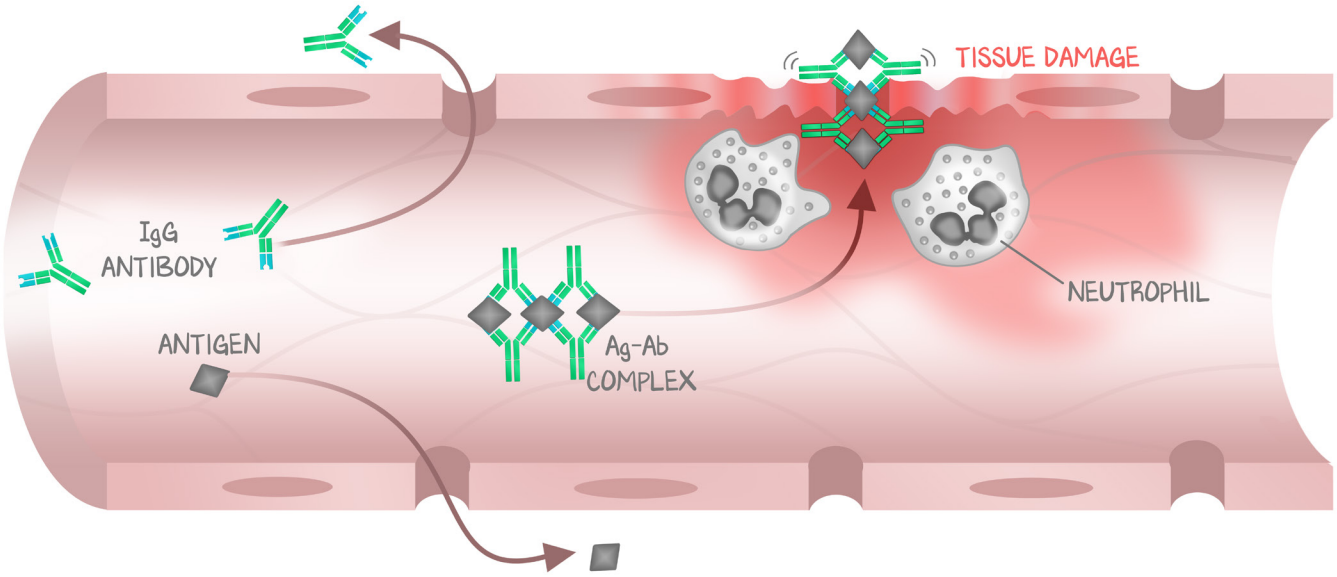

Figure 11.3: Immune-Complex Deposition Hypersensitivity
Immune-complex is about antibodies, but about antibodies to *circulating* antigen. When not complexed, they won't get stuck and won't deposit in tissue. When the antibody-antigen complex forms, the complex is too big to pass through where the components might have been able to fit through. It can't get through the usual filters anymore, and gets stuck. The innate immune system comes to clear it out, often injuring/taking with it whatever organ it happened to get stuck in. It is systemic damage mediated by antibodies against circulating antigen.

Not Antibody Mediated at All: T-Cell Induced

This is the most difficult to explain because so much can do it. It's called **delayed hypersensitivity** or **T-cell-mediated hypersensitivity**, but—unlike all the other types we've discussed already—it's definitely **NOT antibody-related**.

T cells recognize an antigen, release cytokines, and activate macrophages and inflammatory mediators (cytokines) that inflame that organ. That organ gets destroyed. When macrophages appear at the site of inflammation, these APCs present via MHC-2 to $CD4^+$ T cells, which induce more macrophages. If the response is carried out by cytokines, the T cell detects a problem via MHC-1 and induces inflammation. In the next section, we'll see that it's best to memorize the list of diseases that are antibody mediated and T-cell induced, rather than try to deduce the type of reaction based on the presentation of disease.

DISEASE/ PROCESS	ANTIGEN	SYMPTOMS
Tuberculin	PPD antigens	Indurated skin lesion
Contact dermatitis	Metals, latex, plants (poison ivy, oak)	Lesions in the shape of the contact
Hashimoto's	Unknown	Hyper- then hypothyroidism
Multiple sclerosis	Myelin sheath	FND separated in space and time
Type 1 diabetes	β cells of pancreas Glutamic acid decarboxylase	Polydipsia, polyuria, polyphagia DKA/coma
Crohn's	Unknown antigen	Diarrhea, abdominal pain lesions throughout GI tract from mouth to anus
Ulcerative colitis	Unknown antigen	Bloody diarrhea, abdominal pain, colon only

Table 11.4: T-Cell-Induced Diseases
A list of disease processes, the antigen they recognize, and the resultant symptoms. If working towards Immunology mastery only, memorize this chart. If you are at OME for a complete education, skip the memorization of this table and learn the diseases in their corresponding Organ Systems, where they should be learned.

How Do You Predict Which Type of Hypersensitivity It Is?

1. Is there bronchoconstriction, vasodilation, urticaria, rhinitis/conjunctivitis, or symptoms of GI hypermotility? It's IgE-mast-cell.
2. Is it systemic with destruction of various organs such as joints, kidneys, and lungs? Immune-complex deposition.
3. Is there reduced or hyper functioning of the organ without destruction? Antibody mediated.
4. Beyond that . . . if there's destruction or inflammation, memorize whether it's antibody mediated or T-cell regulated. Because antibody-induced destruction is by complement, phagocytosis, or inflammation. T-cell induced destruction is by macrophages and inflammation. But this information can't be used to predict the symptoms from hypersensitivity, and the syndrome can't be used to predict hypersensitivity. Once again, you'll have to memorize some of these, as you can't always deduce or predict the mechanism based on the symptoms/disease or the symptoms/disease based on the mechanism.

Memorizing Types

Mast cell; IgE-mast-cell mediated	Type 1
B cell; antibody mediated (directly against tissue that stays in place)	Type 2
B cell; immune-complex mediated (Ab binds to a cell/tissue that circulates and gets stuck in another part of the body)	Type 3
T cell; delayed-type hypersensitivity (NO antibody)	Type 4

Table 11.5: Mechanism to Type Number

So hey, it turns out that we taught these forms of hypersensitivity in the order they increment by type. You may have to answer "IgE-mediated" or "type 1 hypersensitivity"—both choices are fair game. Stick to mechanisms; memorize as little as possible.